CLAIM STATUS

Claims 27, 54-60, 63 and 64 were previously cancelled. Claims 1, 4-10, 13, 16, 28, 31-37, 40, 43, 46, 47, 61, 62, 65, 66, 68 and 69 are amended for clarity. No new matter has been added.

Claims 1-26, 28-53 and 61, 62, and 65-70 are pending.

REMARKS

35 U.S.C. § 112, Second Paragraph – Indefiniteness Rejection

The Examiner rejected claims 1-26, 28-62, 65-70 under 35 U.S.C. § 112, Second Paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner rejected claims 1-26, 28-62 and 65-70 because of the interchangeable use of terms "monitoring movement" and "assaying movement." Applicant disagrees. Nonetheless, Applicant replaced the term "assaying movement" in claim 66 with the term "monitoring movement" so that the terminology in claim 66 is consistent with the terminology of claims 1, 28 and 69. In view of the amendment to claim 66, Applicant requests that the indefiniteness rejection of claims 1-26, 28-62 and 65-70 be withdrawn.

Also, the Examiner rejected claim 66 as indefinite because, according to the Examiner, the method is drawn to a "first population comprising the first selected chemoattractant receptor" and a "second population comprising the second selected chemoattractant receptor" where the claim upon which claim 66 depends (i.e., claim 1) recites a single population expressing two different chemoattractant receptors. The Examiner concluded that the metes and bounds of claim 66 cannot be determined. Applicant disagrees with the Examiner. Nonetheless, to expedite the prosecution of the instant application, Applicant amended claim 66 to clarify that following the initial screen using the BiRAM assay that employs a single population of cells that includes two known chemoattractant receptors, as defined by claim 1, a candidate antagonist may be screened using RAM assay that employs one cell population (i.e., "a second cell population") that includes the first known receptor and another cell population (i.e., "third cell population") that includes the second known chemoattractant receptor.

Applicant points out that amended claim 66 is definite because the claim clearly states that a second cell population comprises the first chemoattractant receptor, which was present on the first cell population as introduced in claim 1; and a third cell

population comprises the second chemoattractant receptor, which also was present on the first cell population, as introduced in claim 1. As such, it is clear that, although the two chemoattractant receptors for use in the BiRAM assay were expressed in a single cell population, for re-screening purposes in RAM assays, the two chemoattractant receptors are expressed in two separate cell populations (i.e., the second and third populations, respectively). Applicant believes that amended claim 66 is clear and requests that the indefiniteness rejection of claim 66 be withdrawn.

35 U.S.C. § 112, First Paragraph – Enablement Rejection

The Examiner rejected claims 1-26, 28-53, 61, 62, 65-68 and 70 under 35 U.S.C. § 112, First Paragraph, as failing to comply with the enablement requirement because the claims contain subject matter that was not described in the specification in such a way as to enable one skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant disagrees with the Examiner. Applicant asserts that the specification fully enables the scope of the claims 1 and 28 and any claims dependent thereon for the following reasons.

At the outset, Applicant respectfully points out that, generally, the BiRAM and MultiRAM assays are directed to a method of quickly identifying potential antagonists for chemoattractant receptors from a large pool of compounds with unknown antagonist activity. Once a hit or hits are identified, the hits can be further tested in any conventional cell migration assay, uniRAM assay, calcium mobilization assay etc., to determine which of the chemoattractant receptors are specifically reacting with the hit compound.

Throughout the specification, Applicant provides ample description of BiRAM and MutiRAM assays for use in identifying non-specific candidate antagonist hits to the chemoattractant receptors selected for use in the assays. See, pages 18 through 21, first paragraph for BiRAM assay; and pages 21, second paragraph, through page 22, lines 1-4 for MultiRAM assay. The instant specification also includes actual examples

describing how the BiRAM and MultiRAM assays can be performed. For instance, in Example 8 at pages 39-41 of the instant specification, Applicant describes an actual experiment where *known* antagonists were used in the assay to validate that the BiRAM assay works and is able to quickly identify possible antagonists.

As evidence that the BiRAM may be used to also identify *unknown* chemoattractant receptor hits as asserted by Applicant, Applicant herein attaches a declaration of the inventor Dr. Wei as Exhibit I and Exhibits labeled A-B, as part of the declaration of the inventor Dr. Wei Exhibit I hereto. The declaration provides evidence of the patentability of the claimed invention.

Specifically, Applicant repeated the experiments described in Example 8, however this time 92 *unknown* compounds (i.e., candidate antagonists) were tested. As claimed by the Applicants, a cell population (THP-1 cells) comprising the first and second chemoattractant receptors (CCR1 and CCR2 receptors) and 10μM of each test candidate antagonist (92 samples) were placed in the upper chamber of a cell migration apparatus. Inhibitory concentrations of the ligands for the CCR1 and CCR2 receptors, MCP1 and MIP1α, respectively, were placed in the lower chamber of the cell migration apparatus. Duplicate positive control wells containing 1nM MCP1 (for CCR2) or 0.5nM MIP1α (for CCR1) were also included on the plate. Following incubation, the BiRAM assay was terminated and the THP-1 cells that migrated to the lower chamber of the cell migration apparatus in response to the antagonist compounds were quantified by CyQuant assay.

Exhibit A illustrates data obtained from the BiRAM assay described above designed to simultaneously test at least 92 test candidate antagonists on a 96 well plate. As shown in the top panel of Exhibit A, a 'hit' antagonist, CMP2145, was identified using the BiRAM assay. The CMP2145 compound was recognizable from its enhanced signal over the background. The positive controls (i.e., MCP1 and MIP1α) are also marked in the figure. In the bottom panel of Exhibit A, RAM index (RI) was plotted. RI is calculated by dividing the signal for each of the test compounds by the average signal of the 92 test wells. The CMP2145 compound was identified as a

potential antagonist of either the CCR1 or CCR2 chemoattractant receptor. Thus, the BiRAM assay was used to quickly narrow a field of 92 possible antagonists to a single candidate.

To determine whether the CMP2145 compound is an antagonist of CCR1 or CCR2, the CMP2145 was further assayed in a conventional migration assay, similar to one described in Example 1 at pages 32-33 of the instant application. Specifically, THP-1 cells expressing CCR2 receptor were exposed to 0.1nM MCP1 in the presence of serially-diluted 'hit' antagonist, CMP2145.

Exhibit B is a figure generated from data obtained from the conventional migration assay described above. As shown in the figure, CMP2145 was able to inhibit the MCP1-induced cell migration of the THP-1 cells expressing the CCR2 receptor. As such, CMP2145 was identified as the antagonist of the CCR2 chemoattractant receptor.

The CMP2145 compound was also tested in another conventional migration assay using THP-1 cells expressing CCR1 receptor and MIP1α. The CMP2145 did not inhibit the MIP1α-induced cell migration of THP-1 cells expressing the CCR1 receptor (data not shown). As such, CMP2145 was not identified as an antagonist of CCR1 chemoattractant receptor.

In addition to a conventional migration assay used in experiment described in the declaration of inventor Dr. Wei, other methods can also allow for discriminating true chemoattractant receptor antagonist hits from the non-specific blockers following the BiRAM and MultiRAM assays (specification at page 25, lines 1-14). These methods include, for example, the RAM assay (specification at page 20, 1st full paragraph, page 22, lines 1-4, and Figs 8 and 9; and U.S. Pat. No. 7,282,338), conventional HTS methods, such as FLIPR™ that measure calcium mobilization, or a cell migration assay (chemotaxis assay) (specification at page 25, lines 1-14), among other known methods.

In summary, Applicant has shown that when following the Examples provided in the specification and using description of the specification, Applicant was able to simultaneously test 92 unknown compounds (i.e., potential antagonists) in a single BiRAM assay and identify one compound out of the 92 screened compounds being tested as an the antagonist of the CCR1, CCR2, or both, which I then confirmed using a conventional migration assay to be an antagonist of only the CCR2 receptor.

In view of aforementioned recital of guidance found in the specification of specific assay methods that can be used to identify candidate antagonists hits of chemoattractant receptors selected for use in the assays and additional data provided by Applicant in declaration of inventor Dr. Wei Exhibit I, Applicant respectfully submits that the enablement rejection of claims 1-26, 28-53, 61, 62, 65-68 and 70 should be withdrawn.

CONCLUSION

Applicant respectfully submits that the present application is now in condition for allowance. Should the Examiner feel a discussion would expedite the prosecution of this application, the Examiner is kindly invited to contact the undersigned at (312) 245-5398.

Respectfully submitted,

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